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Pathophysiology of ANCA-associated vasculitis: Are ANCA really pathogenic? A note of caution

To the Editor: In their recent article, Heeringa and Cohen Tervaert summarized the evidences for the widely accepted conception, that antineutrophil-cytoplasmic autoauntibodies (ANCA), by activating neutrophils, are the "major players" in the pathogenesis of small vessel vasculitis [1]. We feel a note of caution is appropriate.

First, there is no evidence for binding of ANCA to polymorphonuclear neutrophils (PMN) (or monocytes) in vivo: in patients with high ANCA titer, immunoglobulin G (IgG) deposits cannot be detected on PMN, although the target antigen, for example, PR3, could be detected by use of a heterologous antibody (e.g., in the histologic study described in [2], or the the ex vivo analysis of peripheral blood PMN described in [3]).

Second, to the best of our knowledge, the experiments using ANCA for activation of PMN in vitro were perfomed with purified IgG, or with heterologous antibodies, respectively. According to our experience, the affinity of the ANCA for PMN is far too low for binding in the presence of other plasma proteins. With purified IgG, the low affinity binding can be overcome by high input of purified protein. Thus, stimulation of PMN by ANCA may not occur under in vivo conditions.

Third, in the studies with experimental animals (as reported, e.g., in [4]), the antibodies generated against myeloperoxidase (MPO) are not true autoantibodies, because animals deficient for MPO were used for immunization. These animals are not tolerant to MPO, and consequently, lymphocytes with high reactivity towards "self-MPO" will not be eliminated, leading to the generation of antibodies with high affinity binding. In contrast, when self-tolerance is operative (as it is in humans), antibodies with low affinity binding are produced, which will greatly differ with regard to their interaction with potential target antigens.

While these argument do not necessarily rule out a role of ANCA in vasculitis—or of the PMN—they challenge the current model of ANCA-mediated PMN activation as a major pathogenic factor.

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Reply from the Authors

We would like to respond to the issues raised concerning our recent paper on the pathogenic potential of ANCA [1]. First, it is stated that there is no evidence for binding of ANCA to PMN in vivo. In our view, such studies would be technically very challenging, and multiple reasons can be given for a negative outcome of such studies. Among others, these include the rapid clearing from the circulation of ANCA-coated PMNs and the possibility of internalization of the membrane-bound MPO/anti-MPO or Pr3/anti-Pr3 immune complexes.

The second issue concerns the affinity of ANCA for their target antigens on the PMN surface being too low to induce PMN activation in vivo. Although studies have been performed using ANCA containing whole sera [2], purification of the autoantibodies is common practice to avoid confounding PMN activating mediators (e.g., cytokines) that could be present in whole sera. Although it is difficult to directly translate the results from such in vitro studies to the in vivo situation in patients, they clearly indicate that ANCA, under the right circumstances, can activate PMN. In our view, this probably does not occur systemically but locally when PMNs have bound to endothelial cells. Other factors (infection?) are needed initially to create a proinflammatory environment, resulting in PMN priming and adherence to activated endothelium.